

Conference on 'Future food and health' Symposium II: Diet–gene interactions; implications for future diets and health

Personalised nutrition: ready for practice?

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The efficacy by which dietary interventions influence risk markers of multi-factorial diseases is mainly determined by taking population-based approaches. However, there exists considerable inter-individual variation in response to dietary interventions, and some interventions may benefit certain individuals or population subgroups more than others. This review evaluates the application of nutrigenomic technologies to further the concept of personalised nutrition, as well as the process to take personalised nutrition to the marketplace. The modulation of an individual's response is influenced by both genetic and environmental factors. Many nutrigenetics studies have attempted to explain variability in responses based on a single or a few genotypes so that a genotype may be used to define personalised dietary advice. It has, however, proven very challenging to define an individual's responsiveness to complex diets based on common genetic variations. In addition, there is a limited understanding of what constitutes an optimal response because we lack key health biomarkers and signatures. In conclusion, advances in nutrigenomics will undoubtedly further the understanding of the complex interplay between genotype, phenotype and environment, which are required to enhance the development of personalised nutrition in the future. At the same time, however, issues relating to consumer acceptance, privacy protection as well as marketing and distribution of personalised products need to be addressed before personalised nutrition can become commercially viable.

Personalised nutrition: Nutrigenomics: Nutrigenetics: Dietary advice: Genetic testing

Population v. individual dietary advice

Traditionally, foods have been regarded as sources of the energy, vitamins and minerals required to prevent malnutrition. The Committee on Medical Aspects of Food and Nutrition Policy has set dietary reference values for nutrients and energy intakes that are needed each day to maintain optimal health and for maintenance of normal physiological functions⁽¹⁾. In the UK, the Eat Well Plate has been developed as a population policy tool to define the government's recommendations on healthy diets, and other countries have developed similar initiatives. However, dietary reference values are very much based on requirements for population groups and not for individuals. Therefore, someone's intake of a nutrient could lie lower than the reference nutrient intake level and not lead to a

nutrient deficiency, or the other way round, because requirements differ between persons.

Today, 65 % of the world's population lives in a country where overweight and obesity kills more people than underweight⁽²⁾. Diet is therefore considered as a primary prevention strategy to reduce the risk of chronic disease development, for instance CVD or cancer. The primary prevention population strategy aims to reduce the risk and incidence of disease by favourably shifting disease risk factors in the entire population. A population-wide reduction in risk factors, which may be accomplished through adoption of healthier diets, could be responsible for significant reduction in CVD, which has happened in developed countries over the past few decades⁽³⁾. The epidemiologist Geoffrey Rose highlighted the importance of the primary prevention population strategy, but also

composed the 'prevention paradox' or the 'Rose paradox', which states that a lifestyle measure that reduces risk in an entire population may offer little benefit to the individual⁽⁴⁾.

The concept of personalised nutrition and the notion that nutritional recommendations for the general population need further differentiation for specific subgroups or consumer segments for individual health management and disease prevention is not new and was already described in the 1970s⁽⁵⁾. Persons distinguished by age or by a particular physiological status; for example, infants or pregnant women, have different nutritional needs. Moreover, patients with allergies or chronic diseases, such as diabetes, dyslipoproteinaemia or liver disease, require special diets. In addition to physiological status, the social, physical and economic environment also plays a role in the choice of dietary components to successfully maintain optimal health⁽⁵⁾.

The need for a more personalised approach to nutrition and dietary advice becomes evident when considering the substantial inter-individual variation in response to dietary interventions, as the modulation of an individual response can be influenced by both genetic and environmental factors. A good example of inter-individual variability in response to an intervention resulting from the influence of both genetic and environmental factors is shown in studies that assessed changes in plasma LDL-cholesterol and TAG concentrations following fish oil intervention for a number of weeks. While the mean change in plasma TAG was -35% , the individual changes ranged from -114 to $+88\%$. While in the entire group of subjects the mean percentage change in plasma LDL-cholesterol was $+7\%$, the actual changes in individuals ranged from -50 to $+61\%$ ^(6,7). Subsequently, although available data are limited, it was shown that, long chain *n*-3 PUFA produce greater lowering of plasma TAG in *APOE2* and *APOE4* carriers relative to the *E3/E3* genotype^(8,7). Limited but consistent evidence indicates that high dose DHA supplementation is associated with increases in LDL cholesterol in *APOE4* carriers^(9,10). Indeed, only when personalised nutrition takes into account a person's specific characteristics, which could be genotype, phenotype, metatype, environment etc, efficacy in terms of promoting health and preventing disease can be maximised.

Modulation of dietary responses by genotypes and metatypes

The past decade has seen a surge in interest in assessing how genetic make-up determines susceptibility to health and disease (nutrigenetics), leading to an increased understanding of the individual's fundamental molecular and metabolic processes that are affected by foods (nutrigenomics). The strongest evidence that dietary responses are influenced by genetics comes from twin studies. Monozygotic twins have shown a high intra-pair similarity in the adaptation to long-term overfeeding and in terms of weight gain and fat distribution⁽¹¹⁾, as well as significantly correlated changes in lipoprotein metabolism and body weight when switching between low- and high-fat diets

despite considerable changes in the twins' baseline physical activity levels⁽¹²⁾. Nutrigenetics and nutrigenomics have now created new opportunities to link genetic testing with nutritional advice as a result of a risk-benefit analysis of dietary components on an individual basis⁽¹³⁾, to further help ameliorate nutrition-associated diseases.

One of the first applications of nutrigenomic testing has been the diagnosis of monogenic conditions responsible for a single phenotype, such as for example genetic lactose intolerance. Lactose intolerance is a consequence of intestinal lactase deficiency, resulting in an adverse reaction to products containing lactose, a carbohydrate found in milk and other dairy products⁽¹⁴⁾. In many cases, genetic testing may not be required for monogenic disorders, as the characteristics of the phenotype is usually sufficient basis for deciding on starting a dietary intervention. However, for complex polygenic traits, such as hypertension or diabetes, it is much more challenging to find evidence for the involvement of genes in disease development, and subsequently for the susceptibility of a person, based on their genotype, to modulate disease development through consumption of a complex diet. For instance, there is a range of SNP that have been found to be associated with an increased disease risk of CVD outcomes, and therefore these are believed to be involved in its pathogenesis⁽¹⁵⁾. At the same time, development of CVD is known to be affected by intervention with diets containing many different bioactive nutrients, which can be quantified through measurement responses in multiple hard and intermediate disease outcome measures (e.g. all cause mortality, fatal CHD, non-fatal myocardial infarction, stroke, angina, coronary revascularisation, congestive heart failure, but also blood pressure, weight, serum cholesterol, LDL cholesterol, HDL cholesterol, TAG, C-reactive protein, etc.). The extent to which such responses are affected by a specific diet in single individuals could depend on individual genotypes. We have learned that the predictive value of a single genotype is small compared with that of the family history of a person, risk scores or other known risk factors when considering complex diseases⁽¹⁵⁾. Indeed, multiple minor genetic differences could be modulated by multiple food bioactives, usually with a low receptor affinity, resulting in multiple minor changes in gene expression and negligible changes in the phenotype. In order to disentangle this complexity we need a more detailed understanding of how genotype interacts with dietary bioactives to produce a phenotype⁽¹⁶⁾, supported by significant research investment in whole genome sequencing and bioinformatic initiatives. In addition, it will require the development of large interdisciplinary research consortia and a move to much larger human intervention studies, albeit that this may result in less accurate dietary information in order to enhance workability⁽¹⁷⁾.

The genetic responsiveness to diet is not necessarily the only or main denominator of personalised nutrition. Indeed, the EU-funded project LIPGENE clearly showed that 'metatypes', i.e. an individual's distinct metabolic response to a specific intervention, may also be a good predictor of personal outcomes, with the most reliable signatures being related to different combinations of metabolic markers and cytokine signatures, sometimes

combined with genotypes^(18,19). For example, metabolic phenotyping, using *k*-means clustering (a method of cluster analysis which aims to partition *n* observations into *k* clusters in which each observation belongs to the cluster with the nearest mean) and ¹H NMR metabolomic analysis, was successfully applied in a dietary intervention to identify responders to vitamin D supplementation in terms of the metabolic syndrome. One of the identified phenotype clusters, characterised by lower serum 25(OH) vitamin D and higher levels of adipokines, showed the most distinct beneficial response to the vitamin D supplementation, resulting in a significant decrease in levels of insulin and C-reactive protein, as well as homeostatic model assessment scores. In contrast there was no effect of supplementation on the measured markers of the metabolic syndrome in the total population⁽¹⁸⁾. In another study, levels of complement component C3, a novel cardiometabolic marker of inflammation, appeared to modulate the relationship between dietary fat intake, abdominal obesity and smoking with metabolic syndrome risk. Indeed, higher intake of dietary saturated fat was related to increased levels of plasma glucose, C-reactive protein and abdominal obesity among subjects with high C3 concentrations⁽¹⁹⁾. These data indicate that clusters of outcomes or multiple factors, rather than individual biomarkers, are needed in order to fully appreciate health benefits through a dietary solution.

Development of diet and lifestyle assessment tests

The role of common genetic variations and metabolotypes on health outcomes, particularly in determining an individual's responsiveness to particular dietary patterns, has continued to expand and develop in recent years. Alongside the appearance of the first scientific studies on this subject, a number of early-stage companies (e.g. Sciona, Interleukin Genetics) have focused on developing diet and lifestyle assessment tests for the consumer market, using human genetic information to identify and potentially help manage the risks associated with heart health, bone health, antioxidant and detoxification, inflammation and insulin resistance. In addition, several food ingredient companies have begun investing in the area of personalised nutrition.

Introduction of genetic tests seems premature, however, especially when considering the fact that any recommendations and decisions may be based on insufficient or even inadequate scientific data. Robust and validated data are difficult to obtain, because of the limited availability of biomarkers of health as well as the high cost of human nutrigenomics intervention studies⁽²⁰⁾. However, companies argue there are significant benefits of genotype-based personalised nutrition. First, genotyping offers the prospect of starting early in the prevention of the disease, potentially by adapting to healthier diets. This is particularly important for diseases in which the development of the pathology takes some time before the first complications appear, such as in type 2 diabetes or osteoporosis. Second, targeted early dietary intervention would save resources and help those who would be most likely to benefit. Finally, an individual with an elevated disease risk may,

based on genetic information, have a higher motivation to comply with dietary advice than when given general advice⁽²⁰⁾. Indeed, tailoring information to an individuals' situation is more effective in influencing health behaviour than provision of general information. This was illustrated in a recent paper which showed that a combination of personalised goal setting, 'cook and eat' sessions and education was more effective in attaining healthier food choices than education only, or 'cook and eat' sessions only⁽²¹⁾. Furthermore, high-perceived susceptibility is known to influence motivation for individual behaviour change, albeit that a successful outcome is dependent on the availability, accessibility and affordability of health assessments, advice and healthy food, social support of medical doctors⁽²²⁾.

The implementation of personalised nutrition automatically means that more responsibility is given to the individuals rather than the medical/health care professionals. Currently, consumers can take direct-to-consumer genetic tests providing information on genetic factors that could influence reactions to food and reveal the level of susceptibility to chronic disease development. These tests have not undergone clinical evaluation and can be ordered directly via the internet. Individuals can make their own interpretation of results without having to visit health care professionals. The health value and personal ramifications of this remain unclear⁽²³⁾. A recent report from the Nuffield Council on Bioethics has stated that personalised medicine, or personalised nutrition, requires users to take responsibilities. However, individuals taking the test may not be in a position to properly assess the implications of the outcomes of the testing⁽²⁴⁾. Learning of an increased risk of developing chronic diseases can lead to adverse emotional impacts and anxiety. Direct-to-consumer genetic testing does not offer counselling, which is a crucial component of the genetic risk-assessment process, broadly recommended in guidelines issued by professional societies where clinical tests are undertaken⁽²⁵⁾. Also, in most cases, claims for an individualised diagnosis and treatment can be overstated, but this cannot always be judged properly by the individual who is taking the test. Because of varying regulatory oversight in different countries, consumers are warned that personal data may be used by 'interested third parties' such as employers, insurance companies and the companies releasing the genetic test results. These risks can be contained by laws preventing the disclosure of information to third parties or permitting genetic tests through health care professionals only⁽²³⁾.

Personalised nutrition – ready for practice?

In most European countries, eating behaviour does not match with the national recommendations. Over the years some improvements have been observed, but overall, diets still contain too much saturated fat, sugar and salt and insufficient vegetables, fruit and fish⁽²⁶⁾. If we have a more extensive understanding of the genotypes, phenotypes and metabolotypes that characterise risk populations, and have the capability to potentially identify specific nutritional requirements to promote optimal individual

health^(27,28), would this help to let individual consumers take up healthier eating patterns? An opinion survey of a representative sample in France, Italy, Great Britain, Portugal, Poland and Germany indicated that 66% of respondents would be willing to undergo genetic testing, and 27% of respondents would follow a personalised diet. However, respondents willing to have a test for personalised diets were more likely to report history of hypercholesterolemia, obesity and high stress levels, and those who indicated that they would not have a genetic test were less likely to report having central obesity. Individuals who were aware that they had health problems associated with the metabolic syndrome appeared particularly favourable toward nutrigenomic intervention⁽²⁹⁾. In general, studies on consumer acceptance of personalised nutrition are scarce. Acceptance of genetic testing and personalised nutrition may not depend on the actual science, but on the consumers' understanding of its implications for their personal health^(30,31).

An important issue to consider is the marketing of personalised foods, which is not necessarily straightforward. Indeed, the concept of personalised nutrition has not yet caused big changes in the food industry. It is estimated that, in general, 50% of new products launched onto the market fail, and the actual number is even higher when products that never reach the consumer are included. Personalised foods are produced at an additional cost, and marketing and distribution of personalised products has to be done for increasingly small consumer segments, which may not be financially viable. From a technical perspective, personalised foods with controlled ingredient formulation will be much more challenging to produce. Any changes in production patterns, therefore, will be based on food choice, and not food production^(30,31).

In conclusion, most impact on health and disease prevention could be achieved in the short term if personalised nutrition focused on helping individuals to make healthy dietary choices from existing natural products. This should, for the moment, be based on population dietary advice but where possible, also take into account environmental factors and individual genotypes and metabolotypes, where scientifically justified. Importantly, the efficacy of such an approach can only be guaranteed if we improve our understanding of how individuals can be educated to sustain favourable lifestyle changes for a longer period of time.

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